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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,776	03/29/2004	David F. Muir	UF-336XC3D1	4996

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EXAMINER

AFREMOVA, VERA

ART UNIT	PAPER NUMBER
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1657

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/812,776

Applicant(s)

MUIR, DAVID F.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4,6-23,30-40 and 42-123 is/are pending in the application.
- 4a) Of the above claim(s) 57-115 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-4,6-23,30-40,42-56 and 116-123 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 7/31/06; 9/05/06
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- ☐ Notice of Informal Patent Application
- ☐ Other: ____.

DETAILED ACTION

Claims 1-4, 6-23, 30-40, 42-56 and 116-123 as amended (7/31/2006) are under examination in the instant office action.

Claims 5, 24-29 and 41 are canceled by applicant.

Claims 57-115 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected groups of inventions. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

Claims 1-4, 6-23, 30-40, 42-56 and 116-123 as amended remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 38 and 116 remain indefinite with regard to the claimed terms "predegenerating" conditions including "degeneration and remodeling" in the lack of specific definitions.

Claims 1, 6, 38, 116 as amended recite effects during intended "use " of the nerve graft but, since the claimed phrase "use" does not set forth any steps involved in that use, it is unclear what applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 6-15, 17-21, 30-40, 42-51, 53-56 and 116-120, 122 and 123 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by La Fleur et al. (IDS reference; J. Exp. Med. 1996, 184:2311-2326) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein method comprises 1) step of culturing the nerve tissue segment in vitro and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and DMEM medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue.

The reference by La Fleur et al. discloses a method for treating mammalian nerve tissue wherein method comprises 1) step of “culturing” the nerve tissue in vitro in DMEM medium comprising various supplements at temperature 37°C for various periods of time including 12, 24 and 2) step of “killing” the nerve tissue by chemical treatment for further extraction of proteins, RNA and other components (page 2312, column 2, par. 1-2). The nerve tissues or nerve segments are held or adhered to plastic dishes and, thus, combined with a generic adhesive. The nerve tissues derived from sciatic nerves that connected to both central and peripheral nervous system tissues.

The cited reference comprises identical active steps of culturing and killing nerve tissues under conditions as presently claimed. Thus, the cited reference anticipates the claimed invention.

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2. Claims 1-4, 6-15, 17-23, 30-40, 42-56 and 116-123 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Lassner et al. (IDS reference; J. Reconstruct. Microsurg. 1995, 11 (6): 447-453) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue in vitro and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and DMEM medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by freezing. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays in vitro and in vivo.

The reference by Lassner et al. discloses a method for preparing a nerve tissue for use as a nerve graft wherein method comprises 1) step of culturing the nerve tissue segments in vitro under culture conditions including temperature permissive for cellular outgrowth or 37°C, time 48 hours and DMEM medium with serum, and 2) step of killing the nerve tissue by freezing at minus 18°C; for example: see page 448, column 2, last paragraph that relates to the second series of experiments. The nerve tissues or nerve segments are held or adhered to plastic dishes and, thus, combined with a generic adhesive. The nerve tissues derived from sciatic nerves that connected to both central and peripheral nervous system tissues. The cited reference also describes neurite outgrowth assays in vitro (figures 5 and 7) and in vivo regeneration upon reimplantation (page 449, col. 1).

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The cited reference comprises identical active steps of culturing and killing nerve tissues under conditions as presently claimed. Thus, the cited reference anticipates the claimed invention.

3. Claims 1-4, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 116, 119, 122 and 123 as amended remain/are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,448,076 (Dennis et al) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue in vitro and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and a medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays in vitro and in vivo.

US 6,448,076 discloses a method for preparing a nerve tissue for use as a nerve graft (entire document including abstract) wherein the method comprises step of culturing *in vitro* the nerve graft in a medium or in a balanced salt solution (col. 3, lines 45-46), step of rendering the nerve graft acellular by chemical treatment (col. 3, lines 47-67 and col. 4, lines 26). The nerve graft is a mammalian peripheral nerve segment (col. 3, line 42). The cited patent discloses the 24-96 hours as time intervals for culturing/treating steps and the same temperature ranges including room temperature as required by the presently claimed method. Thus, the cited patent US 6,448,076 appears to teach the same active steps and the same structural elements in the

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method of making graft as claimed. The acellular nerve grafts were used to repair nerve gap in vivo (col.4, lines 47-60) and results were evaluated in vitro (col. 53-66). The cited patent US 6,448,076 teaches that the nerve graft supported axonal regeneration (col. 6, line 21-24) and, therefore, the nerve graft in the cited method was cultured under "predegenerating conditions that remodel the nerve graft and that increase neurite-promoting activity of the nerve graft upon implantation" within the meaning of the instant claims or under conditions "permissive to the activation" of cells or enzymes of the nerve graft within the meaning of the instant claims.

Therefore, US 6,448,076 anticipates the presently claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 6-23, 30-40, 42-56 and 116-123 as amended remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,448,076 (Dennis et al), La Fleur et al. (IDS reference; J. Exp. Med. 1996, 184:2311-2326), Ide et al. (IDS reference; "Schwann cell basal lamina and nerve regeneration". Brain Research. 1983, 288:61-75) and Evans et al. (IDS reference; Progress in Neurobiology, 1994. Vol. 43, pages 187-233) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue in vitro and 2) step of killing the nerve tissue.

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Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and a medium. Some claims are further drawn to the nerve tissues being mammalian including rodent and human. Some claims are further drawn to step of killing by freezing or by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays in vitro and in vivo.

US 6,448,076 (Dennis et al) is relied upon for disclosure of a method for preparing a nerve tissue graft as intended for implantation (entire document including abstract) wherein the method encompasses steps of in vitro culturing and/or in vitro treating the nerve graft and step of rendering the nerve graft acellular by killing.

In particular, the cited patent US 6,448,076 (Dennis et al) discloses a chemical treatment for making acellular nerve grafts and lacks explicit teaching about rendering nerve graft acellular through killing by freezing. However, Evans et al. teaches freezing and thawing of nerve grafts for making the nerve grafts acellular and non-immunogenic (page 212, col. 2, last par.). The cited reference by Ide et al teaches that basal laminae of Schwann cells rather than living cells play important role in nerve regeneration after implantation of nerve graft (page 62, col. 1, par. 1).

The cited patent US 6,448,076 (Dennis et al) teaches the use of balanced salt solution and dubelco' modified base solutions for graft pre-treatment before acellularization but it lacks explicit teaching about the use of an enriched culture media. However, La Fleur reference teaches that incubation of nerve segments in culture medium supplemented with cytokines

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results in up regulation of TIMP-1 expression and that TIMP-1 protects basement membrane of nerve tissue from uncontrolled degradation after injury (abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute a supplemented culture medium for a buffered salt solution in two-step method of US 6,448,076 (Dennis et al) with a reasonable expectation in success in making nerve tissues as intended for nerve grafts because culturing nerve tissues promotes up-regulation of compounds that protect basement membrane of nerve tissues from uncontrolled degradation after injury as adequately taught by La Fleur et al.

One of skill in the art would have been motivated to kill the nerve graft living tissues in order to avoid tissue rejection upon transplantation as clearly taught by Evans et al. Killing by chemical treatment and killing by freezing are considered to be substitution of equivalents.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 7/31/2006 have been fully considered but they are not persuasive.

With regard to the claim rejection under 35 U.S.C. 112, second paragraph, Applicants argue that the meaning of the term "predegenerating conditions" is clear in view of the specification and meaning in the art (response page 13). Specifically, applicants argues that

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“predegeneration conditions” are that conditions when cellular and molecular mechanisms act to enhance the growth-promoting properties of the basal lamina which would retain the ability to stimulate nerve regeneration after cellular elements have been killed. (Specification, page 7, lines 21-24.) Applicants believe that the culturing conditions of the claimed invention allow the living nerve cells to express chondroitin sulfate proteoglycan-degrading enzymes (CSPG-degrading enzymes) and promote Schwann cell proliferation, as would occur naturally in vivo during the remodeling process of nerve degeneration. (Specification, page 27, lines 20-23.).

However, these definitions are very broad. It also appears as argued that the “predegeneration conditions” are those that provide for remodeling of nerve tissue and that the remodeling of nerve tissues is obtained under “predegeneration conditions”. Thus, the applicants’ definitions are circular and they do not clearly point out any specific parameters for the culture conditions during culturing steps and/or they do not clearly point out any active steps as encompassed by “culturing” step. By the virtue being living and viable, as it would naturally occur in vivo, the living nerve cells in vitro would be capable to proliferate and express same enzymes when they are living and/or viable as the living and viable cells in vivo.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by La Fleur et al. applicants argue that the cited reference teaches effects that are essentially opposite of the present invention since Applicant's understanding of predegeneration involves degradation of CSPG but La Fleur teaches that TIMP-1 preserves CSPGs by protecting against MMPs during in vivo degeneration (response pages 14-15). Arguments are not found persuasive because the cited reference discloses method for making a nerve tissue segment or nerve tissue graft that

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comprises identical active steps that are 1) step of culturing the nerve tissue segment in vitro and 2) step of killing the nerve tissue. The culture conditions including temperature, time and media are identical as claimed. Thus, the final effects with regard to remodeling nerve tissue segment in vitro are the same as intended for the claimed nerve tissue segment due to the use of identical culture conditions whether these culture conditions identified as "predegenerating conditions" or not. Moreover, the cited reference discloses expression of TIMP-1 in the cultured tissue segments and it teaches that "TIMP-1 helps preserve Schwann cell BM (basement membrane), thus, promoting axonal regrowth in vivo", for example: see last line of the reference.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 6,448,076 (Dennis et al) applicants argue (response pages 16-17) that Dennis does not describe a culturing step or a placing step under the permissive conditions recited in the claims 1, 38 and 116 since in the Dennis method the nerve is placed in PBS and then acellularization is carried out; thus, there is no culturing step or a placing step that would necessarily fulfill the express requirements of the claims with regard to cell activation and proliferation, enzyme activity, and degeneration and remodeling as argued. Yet, the claimed media are not materially different from PBS in the rejected claims. Thus, the final effects with regard to remodeling nerve tissue segment in vitro are the same as intended for the claimed nerve tissue segment in vitro due to the use of identical in vitro culture conditions whether or not these in vitro culture conditions identified as "predegenerating conditions" and/or "permissive to degeneration". Applicants argue that the final effects as intended such as increase of neurite-promoting activity of a nerve graft in vivo cannot be considered as inherent effects. In response to applicant's argument it is noted that

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a recitation of the intended use or effects of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, the nerve grafts made by the cited method were implanted and provided for axonal regeneration in vivo (col. 6, line 24). The claimed phrase "increase" neither indicates how much is intended "increase" nor it points out relatively to what this increase is intended or observed.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by Lassner et al. applicants argue (response page 18) that the method of the cited reference involved a cold storage at 4 degree C. However, the cited reference also discloses a second series of experiments that involve steps of culturing in DMEM and subsequent freezing as explained above. Applicants appear to argue that the second series of experiments disclosed by Lassner are intended for histological evaluation. Yet, the active steps are identical as required by the claimed method and the culture conditions are the same within the broadest reasonable meaning of the claimed terms "predegenerating conditions" and/or conditions "permissive to degeneration".

With regard to the claim rejection under 35 U.S.C. 103 applicants appear argue (page 19) that there is no suggestion to combine cited references. However, the cited references are in the same field of endeavor such as method of making nerve grafts intended for repairing nerve damage in vivo and they seek to solve the same problems as the instant application and claims such as provide for nerve grafts intended for nerve damage repair in vivo, and one of skill in the

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art is free to select components available in the prior art, *In re Winslow*, 151 USPQ 48 (CCPA, 1966).

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

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The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

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October 13, 2007

A handwritten signature in black ink, appearing to read 'V. Afremova', with a long horizontal stroke extending to the right.

VERA AFREMOVA

PRIMARY EXAMINER